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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/436,184	11/08/1999	JACK R. WANDS	04930/032001	6241

7590 08/13/2002

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	18

DATE MAILED: 08/13/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/436,184	Wands et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____ .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *10, 13-15, and 39-68* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *10, 13-15, and 39-68* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. The request filed on April 19, 2002 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/436,184 is acceptable and a CPA has been established. An action on the CPA follows.

2. Claims 10, 13-15 and 39-68 are pending and examined on the merits.

Claim Rejections Maintained

3. The rejection of claims 10, 13-15 and 39-68 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting growth of a mammalian tumor cell in culture or a method for inhibiting a mammalian tumor cell line grown in culture, said methods comprising the administration of a HAAH antisense nucleic acid consisting of the full length antisense HAAH cDNA as well as antisense DNA corresponding to exon 1 of the HAAH gene, does not reasonably provide enablement for a method for inhibiting tumor growth in a mammal comprising the administration of a HAAH antisense nucleic acid, or the antisense nucleic acid to the 5' AAH regulatory sequence, is maintained for reasons of record as set forth below

. (A)As drawn to a method of inhibiting tumor growth in a mammal.

An effective therapeutic protocol for the treatment or prevention of the formation of a tumor is subject to a number of factors which enter the picture beyond simply the inhibition of expression of a single enzyme, such as aspartyl beta hydroxylase. Demonstrating the inhibition of aspartyl beta hydroxylase expression in tumor cells cannot alone support the predictability of the method for prevention of or treating said tumor growth through administration of either an antisense nucleic acid or an intrabody directed to aspartyl beta hydroxylase. Tumor growth is a complex and multiple step process that proceeds by the acquisition of successive genetic insults (A. Hagemeijer, Leukemia, 1992, Vol. 6, Suppl. 4, pp. 16-18). The establishment and growth of a tumor is subject to variables beyond the overexpression of a single enzyme. The ability of a host

to suppress and thereby prevent the tumor from establishing itself will vary depending upon factors such as the condition of the host, the type and stage of tumor and the tumor burden.

(B)As drawn to the administration of an antisense nucleic acid in vivo.

Claims 11 is drawn to a method of inhibiting tumor growth in a mammal comprising the administration of an antisense nucleic acid. Claim 15 further embodies the inhibition of a CNS tumor. The specification does not enable the scope of the claims, drawn to inhibition of tumor growth in a mammal for the reasons put forth in paragraph (A) supra. The specification teaches the use of the full length antisense HAAH cDNA as well as antisense DNA corresponding to exon 1 of the HAAH gene were used to decrease the level of expression of the HAAH polypeptide in hepatocyte carcinoma cells, and alter the morphology of the treated cells to resemble a more differentiated phenotype. The specification does not teach the decreased level of expression of the HAAH polypeptide or the alteration of cellular morphology in a tumor in situ. The specification does not teach the decreased level of expression of the HAAH polypeptide, or alterations in cell morphology in any CNS tissue, in vitro or in vivo.

It is recognized in the art that the development of clinically useful antisense strategies for disease therapy is fraught with difficulties, even when the nucleic acid sequence for the target protein is known. Antisense nucleic acids, such as antisense cDNA or antisense exons, that are large and highly charged often interact with a wide variety of untargeted cellular components causing undesirable "non-antisense effects" (A.Branch, Hepatology, 1996, Vol. 24, pp. 1517-1529). Antisense nucleic acids must be optimized for use in patients. Additionally, it is well know in the art that the use of modified anti-sense oligonucleotides on CNS targets are limited by the powerful ability of the blood-brain barrier to exclude such anti-sense oligonucleotide. In order to use anti-sense technology for treatment of CNS pathologies, careful consideration must be made with respect to the target nucleotide sequence within the gene of interest, the choice of backbone modifications for the oligonucleotide, and the presence of special sequence motifs which predispose the oligonucleotide to undesirable non-antisense effects (Broaddus et al,

Methods in Enzymology, 2000, Vol. 314, pp. 121-135). The published data indicates that only a small percentage of the antisense oligonucleotides which are tested in vitro are actually effective in the reduction of the target mRNA, and that the ability of the anti-sense oligonucleotides to bind to a target mRNA cannot be predicted due to the structure and conformation assumed by individual mRNA specie (Broaddus et al, pg. 122). Further, even if the specific structure and conformation of a particular mRNA could be adequately predicted as an isolated molecule in a protein-free environment, it would not anticipate the accessible sites for the anti-sense oligonucleotide in vivo, wherein proteins are available to bind to the mRNA thus obscuring the oligonucleotide binding sites and potentially altering the conformation of the target mRNA. Broaddus et al teaches that a highly empirical approach to the testing of candidate anti-sense oligonucleotides is critical for the establishment of an antisense oligonucleotide as a therapeutic agent for the treatment of patients. This requirement has not been met by the instant specification, therefore, one of skill in the art would be forced into undue experimentation without reasonable expectation of success in order to practice the invention as claimed.

4. Applicant has not provided any arguments to counter the instant rejection.

Conclusion

5. This is a CPA of applicant's earlier Application No. 09/436,184. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
August 1, 2002

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